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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,289	TSUDA ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *10-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-9, drawn to a method of identifying a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor, classified in class 435, subclass 334.

II. Claims 10-13, drawn to a method of identifying a compound useful for the treatment or prevention of neuropathic pain using a microglia inhibitor, classified in class 514, subclass 44.

III. Claims 14-18, drawn to pharmaceutical compositions containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antibody or an antibody fragment, classified in class 424, subclass 9.34.

IV. Claims 14-17,19-21, drawn to pharmaceutical compositions containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antisense nucleic acid, classified in class 514, subclass 44.

V. Claims 22-25, drawn to pharmaceutical compositions containing a microglia-activation inhibitor, classified in class 514, subclass 44.

VI. Claims 26-29, 33-35, drawn to a method of treating or preventing neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antibody or antibody fragment, classified in class 424, subclass 9.34.

VII. Claims 26-28, 30-35, drawn to a method of treating or preventing neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antisense nucleic acid, classified in class 514, subclass 44.

VIII. Claims 36-41, drawn to a method of treating or preventing neuropathic pain using a microglia-activation inhibitor, classified in class 514, subclass 44.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation. The mode of operation of invention I is to identify a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor wherein the inhibition occurs by preventing interaction of a P2X4 receptor agonist and a P2X4 receptor while the function of invention II is to identify a compound useful for the treatment or prevention of neuropathic pain using a microglia inhibitor wherein the inhibition occurs by prevention of microglia activation.

3. Inventions I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of

invention I is to identify a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor while the function of invention III is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antibody or an antibody fragment.

4. Inventions I and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention I is to identify a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor while the function of invention IV is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antisense nucleic acid.

5. Inventions I and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention I is to identify a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor while the function of invention V is to form a pharmaceutical composition containing a microglia-activation inhibitor.

6. Inventions I and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In

the instant case the different inventions have different functions. The function of invention I is to identify a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor while the function of invention VI is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antibody or antibody fragment

7. Inventions I and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention I is to identify a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor while the function of invention VII is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antisense nucleic acid.

8. Inventions I and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention I is to identify a compound useful for the treatment or prevention of neuropathic pain using a P2X4 receptor inhibitor while the function of invention VIII is to treat or prevent neuropathic pain using a microglia-activation inhibitor

9. Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of

operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention II is to identify a compound useful for the treatment or prevention of neuropathic pain using a microglia inhibitor while the function of invention III is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antibody or an antibody fragment.

10. Inventions II and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention II is to identify a compound useful for the treatment or prevention of neuropathic pain using a microglia inhibitor while the function of invention IV is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antisense nucleic acid.

11. Inventions II and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention II is to identify a compound useful for the treatment or prevention of neuropathic pain using a microglia inhibitor while the function of invention V is to form a pharmaceutical composition containing a microglia-activation inhibitor.

12. Inventions II and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention II is to identify a compound useful for the treatment or prevention of neuropathic pain using a microglia inhibitor while the function of invention VI is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antibody or antibody fragment

13. Inventions II and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention II is to identify a compound useful for the treatment or prevention of neuropathic pain using a microglia inhibitor while the function of invention VII is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antisense nucleic acid.

14. Inventions II and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention II is to identify a compound useful for the treatment or prevention of

neuropathic pain using a microglia inhibitor while the function of invention VIII is to treat or prevent neuropathic pain using a microglia-activation inhibitor

15. Inventions III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation. Invention III operates by forming a pharmaceutical composition containing a P2X4 receptor inhibitor that is an antibody or an antibody fragment while invention IV operates by forming a pharmaceutical composition containing a P2X4 receptor inhibitor that is an antisense nucleic acid.

16. Claim 14 link(s) inventions III and IV. Claims 15-17 are generic to groups III and IV. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 14. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C.

121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

17. Inventions III and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention III is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antibody or an antibody fragment while the function of invention V is to form a pharmaceutical composition containing a microglia-activation inhibitor.

18. Inventions III and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention III is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antibody or an antibody fragment while the function of invention VI is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antibody or antibody fragment

19. Inventions III and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of

invention III is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antibody or an antibody fragment while the function of invention VII is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antisense nucleic acid.

20. Inventions III and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention III is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antibody or an antibody fragment while the function of invention VIII is to treat or prevent neuropathic pain using a microglia-activation inhibitor

21. Inventions IV and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation. Invention IV operates by forming a pharmaceutical composition containing a P2X4 receptor inhibitor that is an antisense nucleic acid while invention V operates by forming a pharmaceutical composition containing a microglia-activation inhibitor.

22. Inventions IV and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In

the instant case the different inventions have different functions. The function of invention IV is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antisense nucleic acid while the function of invention VI is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antibody or antibody fragment.

23. Inventions IV and VII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case invention IV is a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antisense nucleic acid while invention VII is a method of treating or preventing neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antisense nucleic acid. The composition of invention IV is not solely usable for treating or preventing neuropathic pain. The composition could also be used to bind the complement of the antisense nucleic acid sequence.

24. Inventions IV and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention IV is to form a pharmaceutical composition containing a P2X4 receptor inhibitor where the P2X4 receptor inhibitor is an antisense nucleic acid while the

function of invention of invention VIII is to treat or prevent neuropathic pain using a microglia-activation inhibitor.

25. Inventions V and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention V is to form a pharmaceutical composition containing a microglia-activation inhibitor while the function of invention VI is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antibody or antibody fragment.

26. Inventions V and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention V is to form a pharmaceutical composition containing a microglia-activation inhibitor while the function of invention VII is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antisense nucleic acid.

27. Inventions V and VIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case invention V is a

pharmaceutical composition with a microglia-activation inhibitor while invention VIII is a method of treating or preventing neuropathic pain using a microglia-activation inhibitor. The composition of invention V is not solely usable for treating or preventing neuropathic pain. The composition could also be used to inhibit microglia activation *in vitro*.

28. Inventions VI and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation. The mode of operation of invention VI is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor that is an antibody or antibody fragment while the mode of operation of invention VII is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor that is an antisense nucleic acid.

29. Claim 26 link(s) inventions VI and VII. Claims 27 and 28 are generic to groups VI and VII. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 26. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional

statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

30. Inventions VI and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention VI is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor wherein the P2X4 receptor inhibitor is an antibody or antibody fragment while the function of invention VIII is to treat or prevent neuropathic pain using a microglia-activation inhibitor.

31. Inventions VII and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different functions. The function of invention VII is to treat or prevent neuropathic pain using a P2X4 receptor inhibitor that is an antisense nucleic acid while the function of invention VIII is to treat or prevent neuropathic pain using a microglia-activation inhibitor.

Species election

32. Claim 7 is generic to a plurality of disclosed patentably distinct species comprising Na^+, K^+ and Ca^{2+}. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species if invention I is elected, even though this requirement is traversed.

33. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

34. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

35. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance,

whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

36. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

37. During a telephone conversation with Janet Cord on May 26, 2004 a provisional election was made with traverse to prosecute the invention of group I, claims 1-9. For the species recited in claim 7, election of Ca^{2+} was made. Affirmation of this election must be made by applicant in replying to this Office action.

38. Claims 10-41 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 102

39. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Tsuda et al.(P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury, *Nature*, 14 August 2003, vol 424 p778-783 and supplemental information).

Claim 1 is drawn to a method of identifying compounds useful for treatment of neuropathic pain comprising the steps of: (a) contacting a cell expressing a P2X4 receptor with a test compound and a P2X4 receptor agonist, (b) determining whether or not the test compound inhibits interaction of the receptor and agonist, and (c) identifying the compound that inhibits the interaction as useful for treatment of neuropathic pain.

Claims 2-9 depend from and further limit claim 1. Claim 2 limits claim 1 by stating the neuropathic pain is tactile allodynia, claim 3 limits claim 1 by stating the cell must be mammalian, claim 4 states that the only P2X receptor present is P2X4, claim 5 limits claim 1 by stating the agonist is ATP or ADP, claim 6 limits claim 1 by stating that step (a) is carried out by pre-incubating the cell and the test compound in the absence of the agonist, claim 7 limits claim 1 by stating that step (b) is carried by measuring the receptor mediated flux of Ca^{2+} ion, claim 8 limits claim 1 by stating that step (a) is carried out in the presence of Ca^{2+} ion and claim 9 limits claim 1 by stating that step (b) comprises comparing the intensity of interaction with a control sample that has not been contacted with the test compound.

Tsuda et al. disclose the use of antagonists of P2X4 receptors to treat nerve-injured rats. In the supplemental information, Tsuda et al. describe the expression of P2X4 receptors in microglia cells and the use of Ca^{2+} ion flux to measure the effects of agonist and antagonists on the cells, disclosing steps (a) and (b) of claim 1 and the limitations of claims 3-9. On page 782 (column 2, last paragraph), Tsuda et al. disclose that P2X4 receptors are involved in tactile allodynia and that blockade of the receptors reverses the allodynia. Tsuda et al. also disclose that P2X4 receptors are a novel therapeutic target for treatment of nerve-injury-induced pain, thus disclosing step (c) of the method of claim 1 and the limitation of claim 2.

40. Claims 1, 3-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Lynch et al. (US 6,242,216, June 5, 2001). Lynch et al. disclose nucleic acids that encode functional human P2X4 receptors, the methods of production and methods of use of

these receptors. At column 20, lines 38-62, P2X4 receptors are expressed on Xenopus oocytes and their response to agonists and antagonists are measured. The measurements described here disclose steps (a) and (b) of the method of claim 1 and the limitations of claims 4, 5, 6, 8 and 9. At column 11, lines 18-30, Lynch et al. disclose that inhibition of agonists can be measured by Ca^{2+} ion flux in mammalian cells, thus disclosing the limitation of claims 3 and 7. At column 12, lines 1-37, the use of cells expressing P2X4 receptors to identify compounds capable of modulating receptor activity and the potential uses for such modulators as therapeutic agents against pain, are disclosed. This discloses step (c) of claim 1. Thus, Lynch et al. disclose the method of claim 1 and all the limitations of claims 3-9.

Claim Rejections - 35 USC § 103

41. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

42. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al. (Pharmacological Characterisation of the Human P2X4 Receptor Using the FLIPR, *Pharmacology Reviews and Communications*, vol. 10, p341-347) in view of Tsuda et al. (Mechanical Allodynia Caused by Intraplantar Injection of P2X Receptor Agonist in Rats: Involvement of Heteromeric $P2X_{2/3}$ Receptor Signaling in Capsaicin-Insensitive Primary Afferent Neurons, *Journal of Neuroscience*, 2000, vol 20, p RC90/1-RC90/5).

Wood et al. teach the characterization of human P2X4 receptor. The receptor is expressed in human astrocytoma cell line 132 1N1, a mammalian cell line. The response of the P2X4 receptor is measured by determining the Ca^{2+} ion flux in the presence of agonist and/or antagonist. Measurements were done with the antagonist incubated with the cell before addition of the agonist. Measurements were also done without antagonist (ie, as described in Materials and methods, with buffer alone). Wood et al. teach that ATP has no effect on non-transfected cells, indicating that the cloned P2X4 receptor is the only P2X receptor present. Thus Wood et al. teach steps (a) and (b) of the method of claim 1 and the limitations of claims 3-9. Wood et al. do not teach that this method can be used to identify compounds useful in the treatment of neuropathic pain.

Tsuda et al. teach that injection of P2X receptor agonists into rats caused mechanical allodynia and that this allodynia could be reversed by pre-treatment with P2X receptor antagonists. Tsuda et al. hypothesized the type of P2X receptor responsible for the results they reported, but were unable to exclude the possibility that other receptors were involved. They state: "..the discovery of new selective antagonists...for each P2X receptor subtype is awaited to clarify our hypothesis". (see page 4) Later in their conclusion (pages 4-5), Tsuda et al. state that P2X receptors are believed to play a role in pain and further state that "...the mechanisms underlying P2X receptor-mediated mechanical allodynia may be one of the determining factors of the mechanical allodynia in these painful states. Elucidation of this pathway may lead to

the discovery of a new class of compounds that suppress mechanical allodynia in pathological pain."

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the method of Wood et al. to identify compounds useful in the treatment of neuropathic pain as taught by Wood et al. Tsuda et al. provided a motivation to do so, teaching a relationship between P2X receptors and pain and stating the desirability of new compounds for the suppression of pain. A person of ordinary skill in the art would have had a reasonable expectation of success in using the method taught by Wood et al. to identify compounds useful in the treatment of neuropathic pain because Wood et al. taught their method to identify antagonists of P2X4 receptors using techniques well known in the art and demonstrate this method actually successfully identifies P2X4 receptor antagonists. Therefore, the invention of claims 1-9 would have been obvious, as a whole, at the time the instant invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Tracy Vivlemore
Examiner

Art Unit 1635

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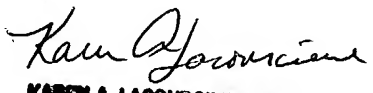
June 15, 2004



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